Synergieffekter av miljögifter

Samverkanseffekter av miljögifter under nyföddhetsperioden

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Samverkanseffekter av miljögifter under nyföddhetsperioden

- Hur kan vi upptäcka om ämnen är skadliga för hjärnans utveckling?
- Har hjärnan en kritisk period under utvecklingen då beteende/funktionella störningar lättare kan induceras?
- Kan kemikalier samverka med varandra och förstärka effekterna – och kan kemikalier och strålning samverka?

Brain development – ”Neonatal animal model”

Gestational Period

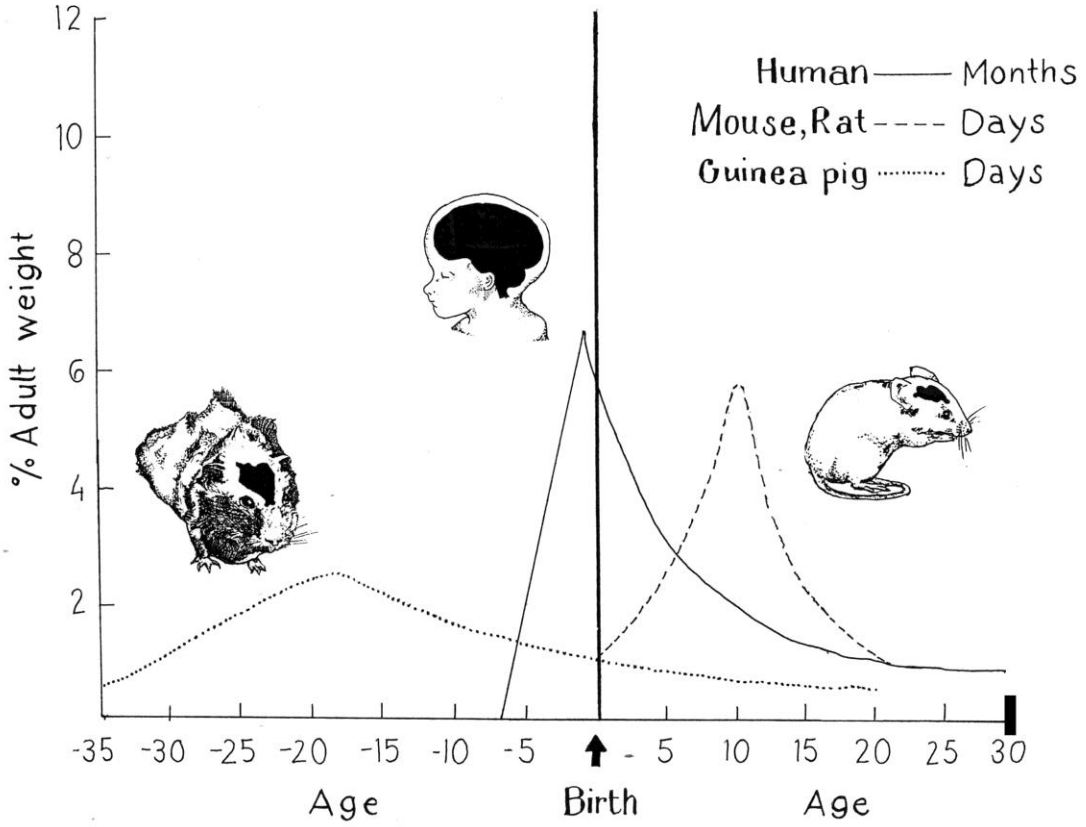
- Human, 9 months
- Embryo, day 1-58 (20%)
- Fetus, day 58-270 (80%)

- Exposure during the fetal period – functional anomalies of CNS and reproductive organs

- Mouse, 20 days
- Embryo, day 1-16 (80%)
- Fetus, day 16-20 (20%)

- Functional anomalies – behavioural, cognitive, motor deficits

Brain Growth Spurt

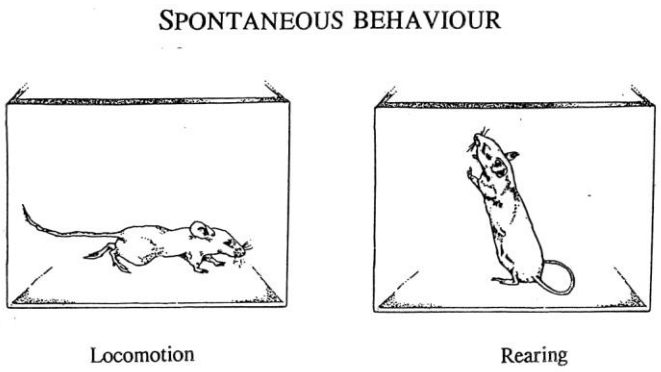


The developing brain during the perinatal and/or neonatal period

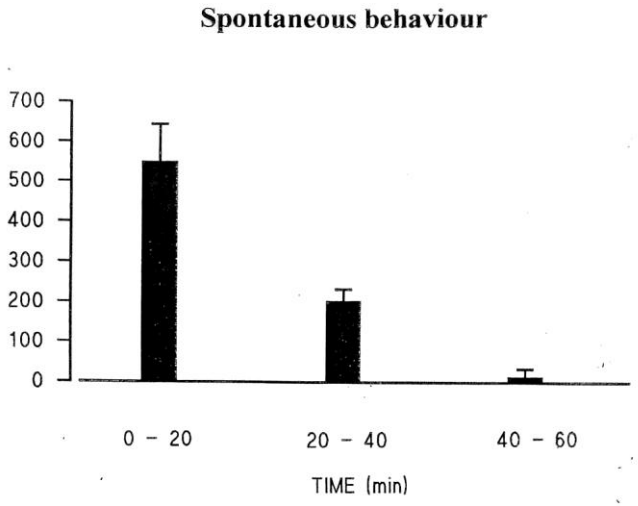
- 15,000 synapses for every cortical neuron
  - 1.8 million synapses/second in first 2 years!
- Cerebral cortex triples in thickness in 1st year
- Sensory and motor neurons must extend to correct brain areas and form correct synapses
- 100,000 synapses are lost every second the first 2 years

Behavioural toxicology: is the study of changes in the behaviour of human beings and animals due to toxic substances.

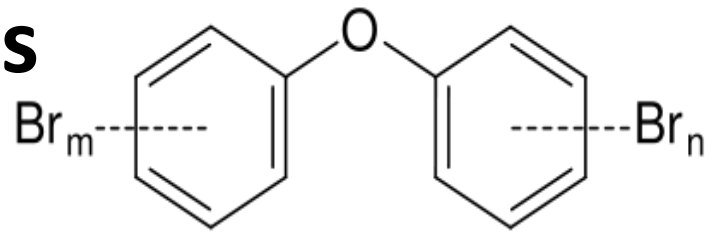
Spontaneous behaviour in a novel home environment: measure integration of sensoric input into a motoric output - cognitive function



Normal spontaneous behaviour

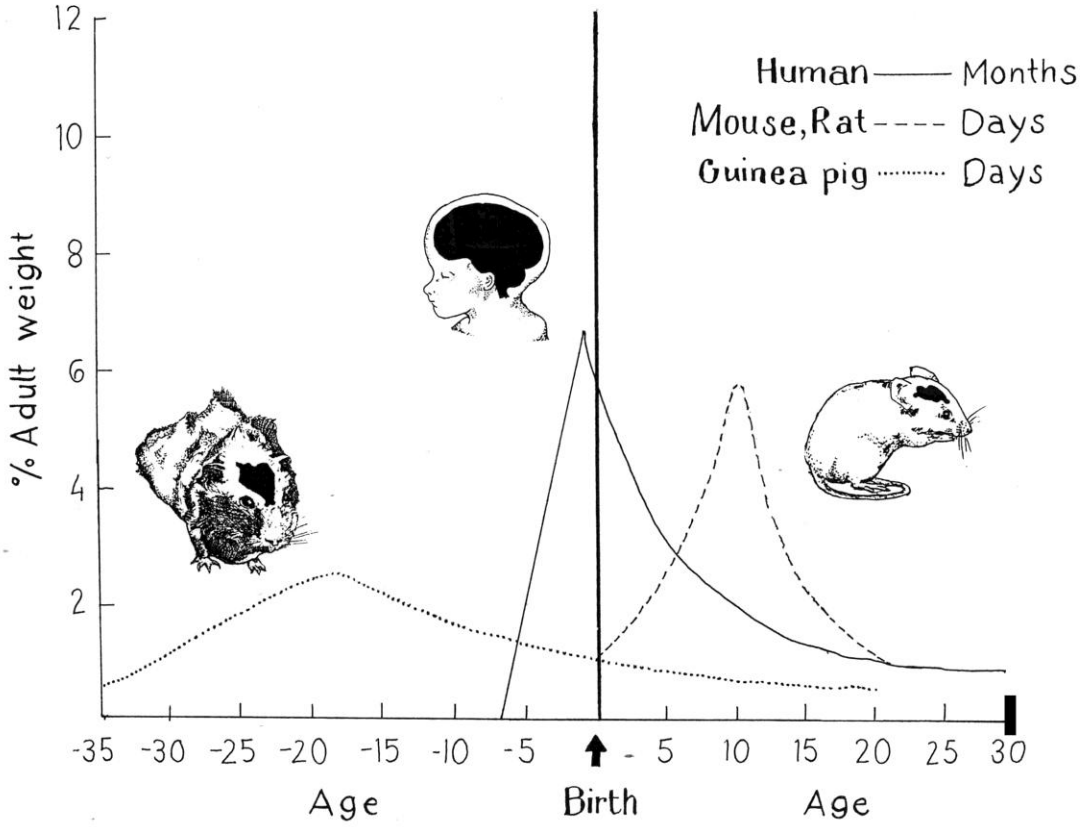


Polybrominated diphenyl ethers (PBDEs) – short facts

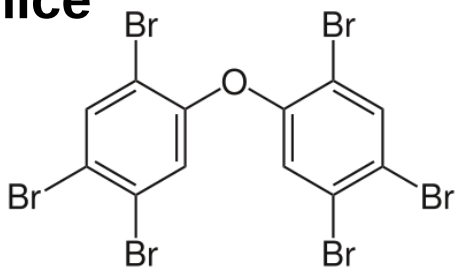


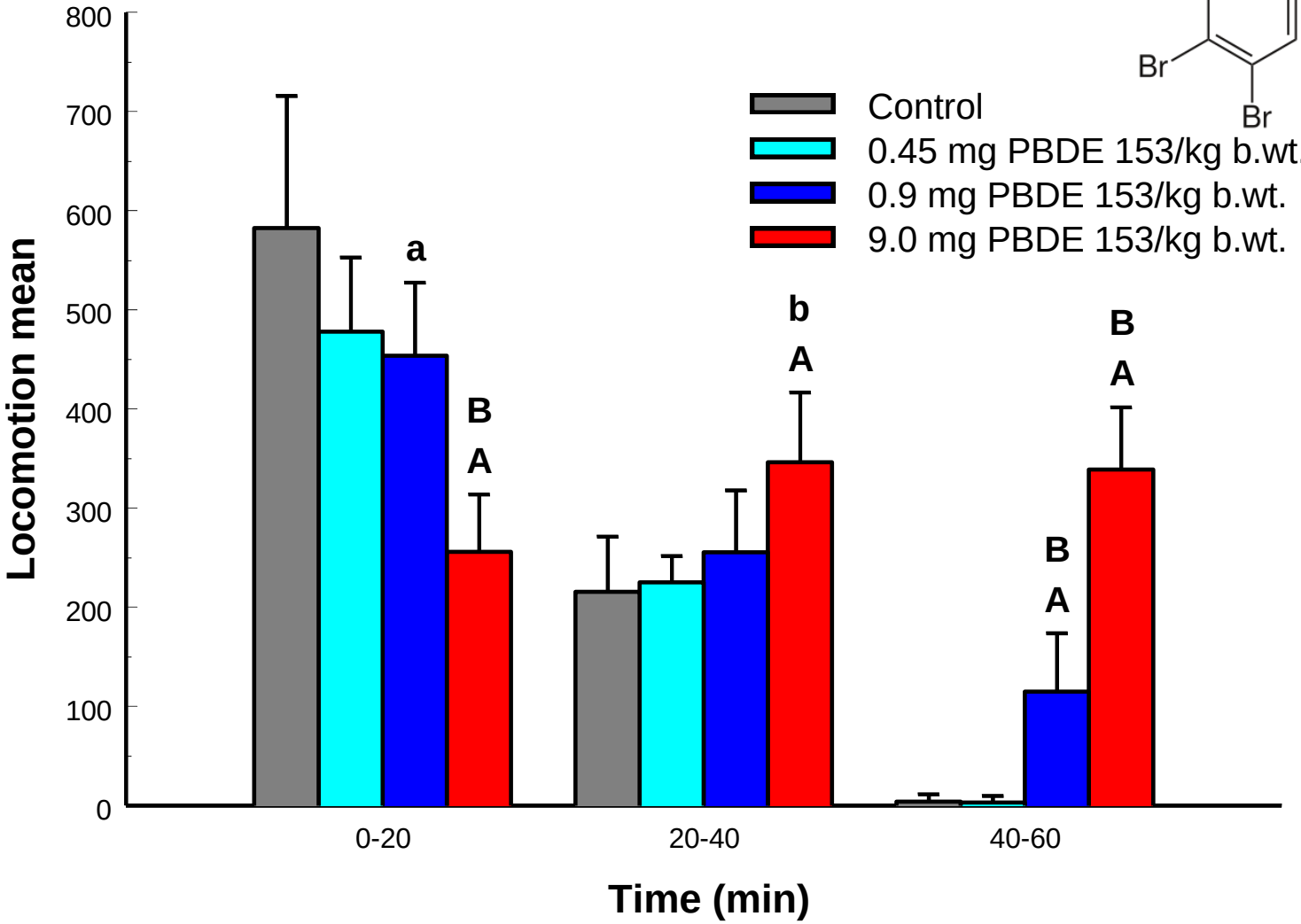
- Used as additive flame retardants in polymer products, electronic equipments, textiles .
- Present in high levels in the environment, human serum, and human mother's milk. Present in house dust.
- Higher levels in children compared to older people, indicate direct exposure to children
- Known to affect several organ systems.
- Induce neurotoxicity in vitro and in vivo, both in utero and neonatally.

Brain Growth Spurt

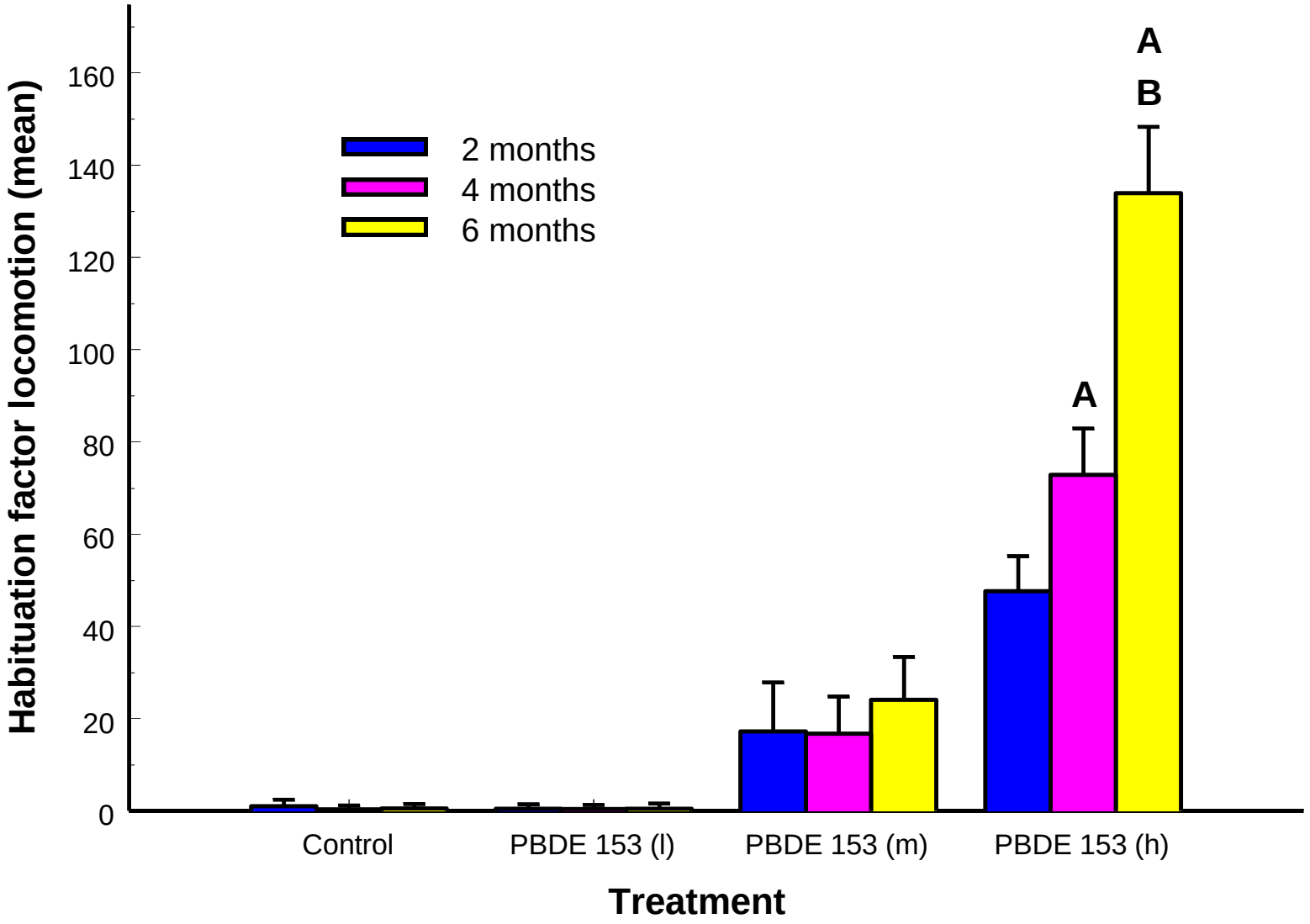


Spontaneous behaviour in 6 months old mice after neonatal exposure to PBDE 153





Habituation factors for locomotion in 2 , 4 and 6 months old mice, after neonatal expoisure to PBDE 153



Samverkanseffekter av miljögifter under nyföddhetsperioden

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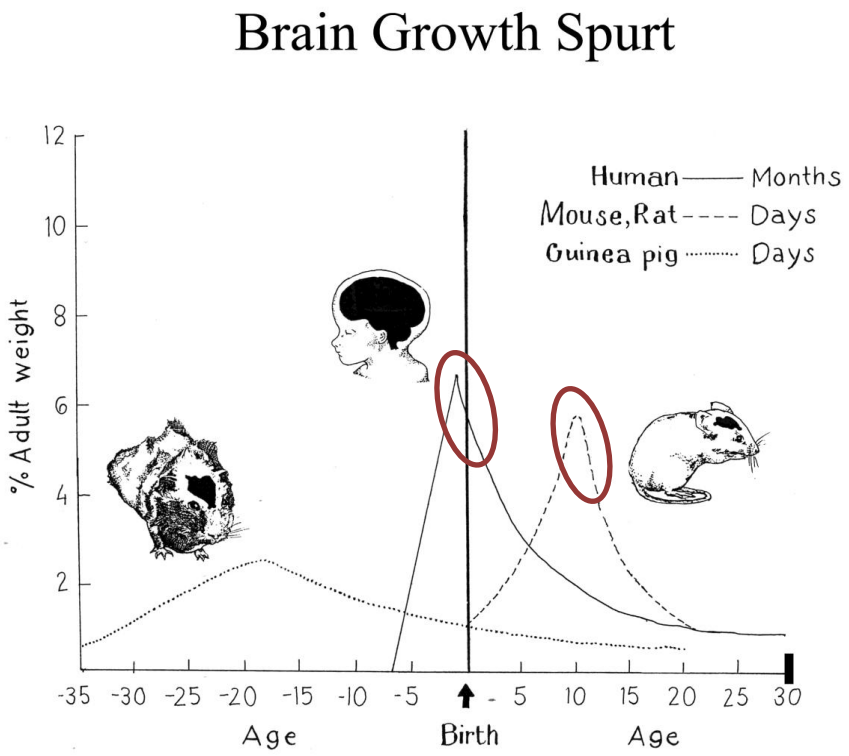
- **Har hjärnan en kritisk period under utvecklingen då beteende/funktionella störningar lättare kan induceras?**
- Kan kemikalier samverka med varandra och förstärka effekterna – och kan kemikalier och strålning samverka?

Developmental neurotoxicity of toxicants and ionising radiation

A critical window



Exposure to :
- **polychlorinated biphenyls (PCBs)[1],**
- **dichlorodiphenyltrichloroethane (DDT)[2],**
- **brominated flame retardants (BFRs)[3],**
- **perfluorinated chemicals (PFC)[7]**
- **ionising radiation[8]**
- **anaesthetics[9]**

And to neurotoxic agents :
- **nicotine[4],**
- **organophosphorous compounds[5],**
- **1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [6]**

→ **Disruption of the adult brain function**
→ **Increased susceptibility in adults**
→ **Protein biomarkers**

→ **Critical window of brain vulnerability around PND 10**

1: Eriksson, 2007 2: Eriksson, 1992 , 7. Johansson, 2009, 8. Eriksson et al. 2010, 9. Pontén et al., 2011
3: Eriksson et al., 2001 and Viberg et al., 2004 4: Eriksson et al., 2000 5: Albohm, 1995 6: Fredriksson et al., 1993

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Interaction between environmental agents (POPs and MeHg) during neonatal brain development affects behaviour and the cholinergic system

Epidemiological studies

-PCB: psychomotor delays, delayed cognitive development, IQ deficits

-MeHg: psychomotor retardation, seizures, developmental delays, mental retardation (Japan, Iraq)

-Faroe Islands (Hg 4.3 ppm), effects on child neurologic development [+ PCB?]

-Seychelle Islands (Hg 5.9 ppm), no adverse effects on child neurologic development

-**Animal studies:** PCB, MeHg

Neonatal exposure

-Neonatal exposure to both PCB and MeHg. *[Fischer et al., Toxicology 2008; 244, 157-165].*

-Neonatal exposure to both PBDE and MeHg. *[Fischer et al., Toxicol Sci 2008; 101, 275-285].*

-Neonatal exposure to both PBDE and PCB. *[Eriksson et al., Toxicol Sci 2006; 94, 302-309].*

Neonatal exposure to ionizing radiation and MeHg. *[Eriksson et al., Neurotoxicology 2010; 31,223-229]*

Experimental design co-exposure PCB 153 and MeHg

NMRI male mice

Neonatal exposure on postnatal day 10,

one single oral dose

Vehicle: 20% fat emulsion

PCB 153: 0.51mg[1.4µmol]/kg bw

MeHg: 0.08mg/kg bw, 0.40mg/kg bw, and 4.0mg/kg bw

PCB 153 0.51mg/kg bw + MeHg 0.08mg/kg bw,

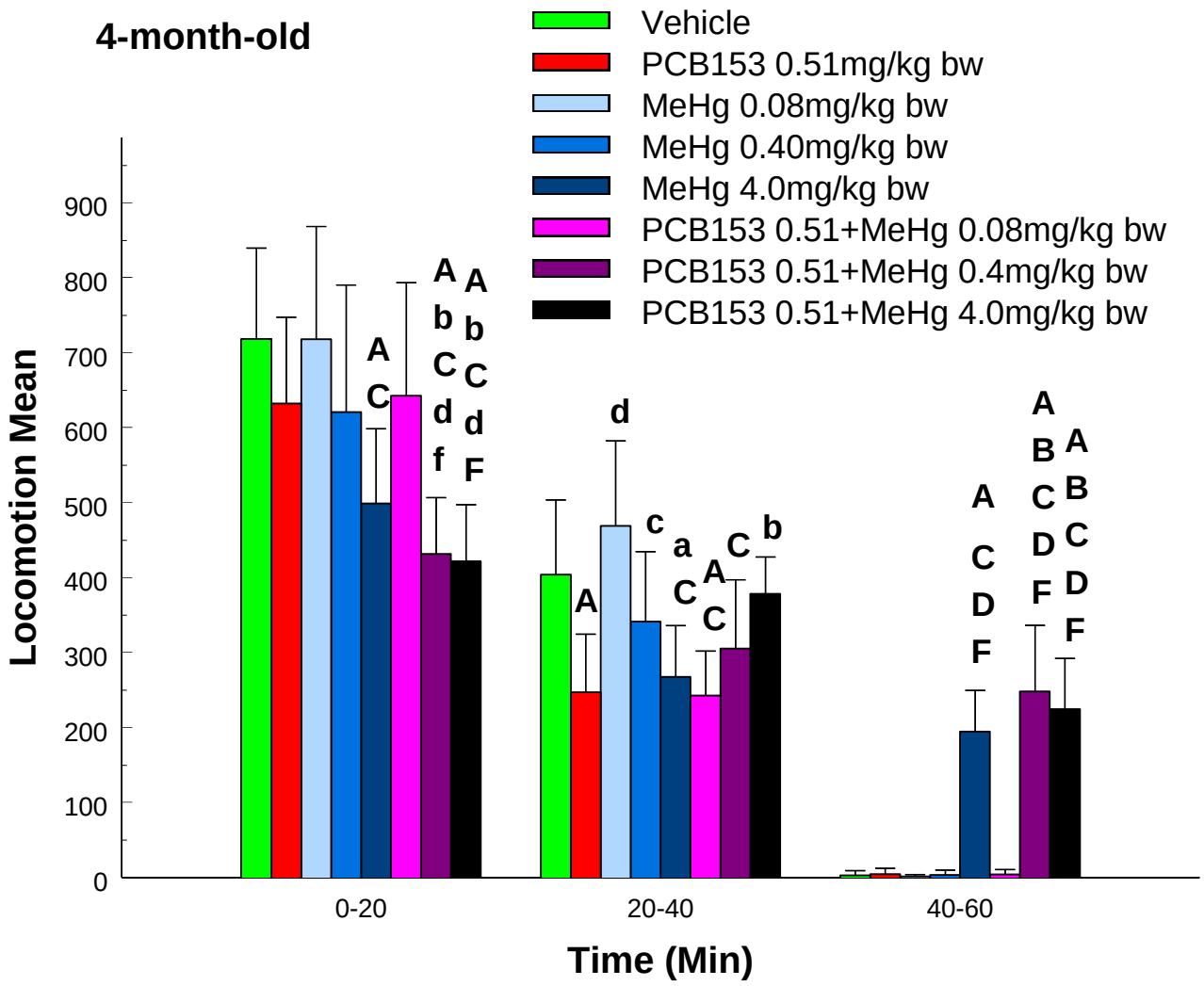
PCB 153 0.51mg/kg bw + MeHg 0.40mg/kg bw,

PCB 153 0.51mg/kg bw + MeHg 4.0mg/kg bw

Spontaneous behaviour: 2-month-old and 4-month-old

Swim maze: 4-month-old

DEVELOPMENTAL NEUROTOXICITY TO CO-EXPOSURE PCB153 AND MeHg, SPONTANEOUS BEHAVIOUR

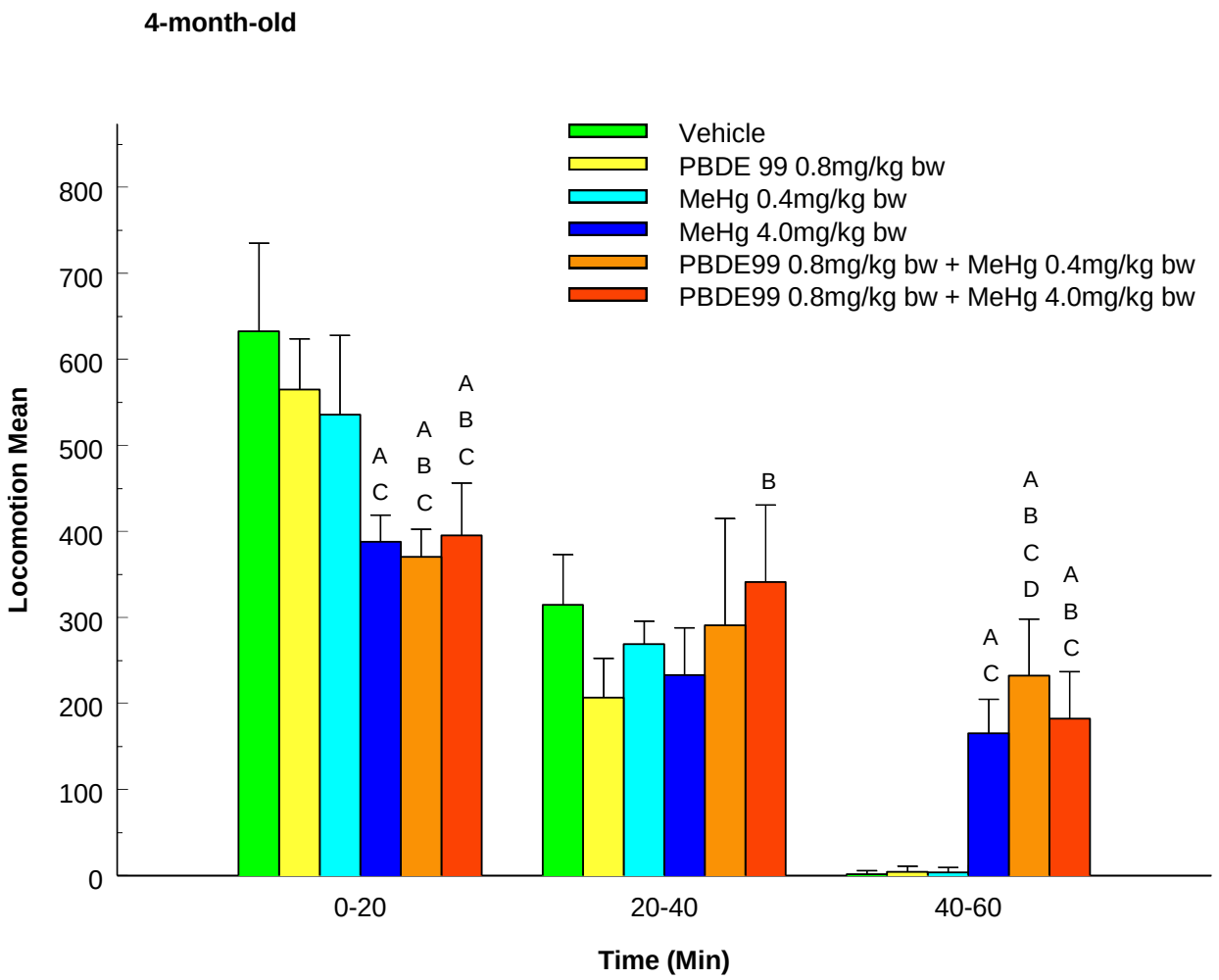


Neonatal exposure to both PBDE 99 and MeHg

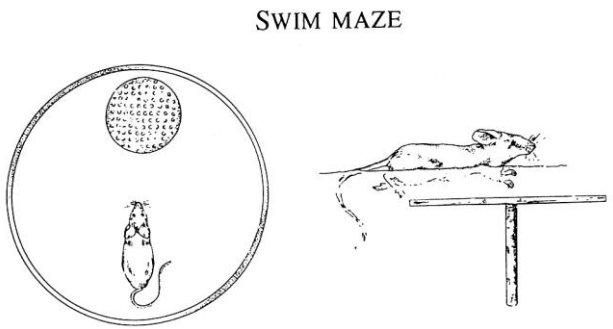
NMRI male mice
Neonatal exposure on postnatal day 10,
one single oral dose
Vehicle: 20% fat emulsion
PBDE 99: 0.8mg [1.4µmol]/kg bw
MeHg: 0.40mg/kg bw, and 4.0mg/kg bw
PBDE 99 0.8mg/kg bw + MeHg 0.40mg/kg bw, and PBDE 99 0.8mg/kg bw + MeHg 4.0mg/kg bw
Spontaneous behaviour: 2-month-old and 4-month-old
Swim maze: 4-month-old

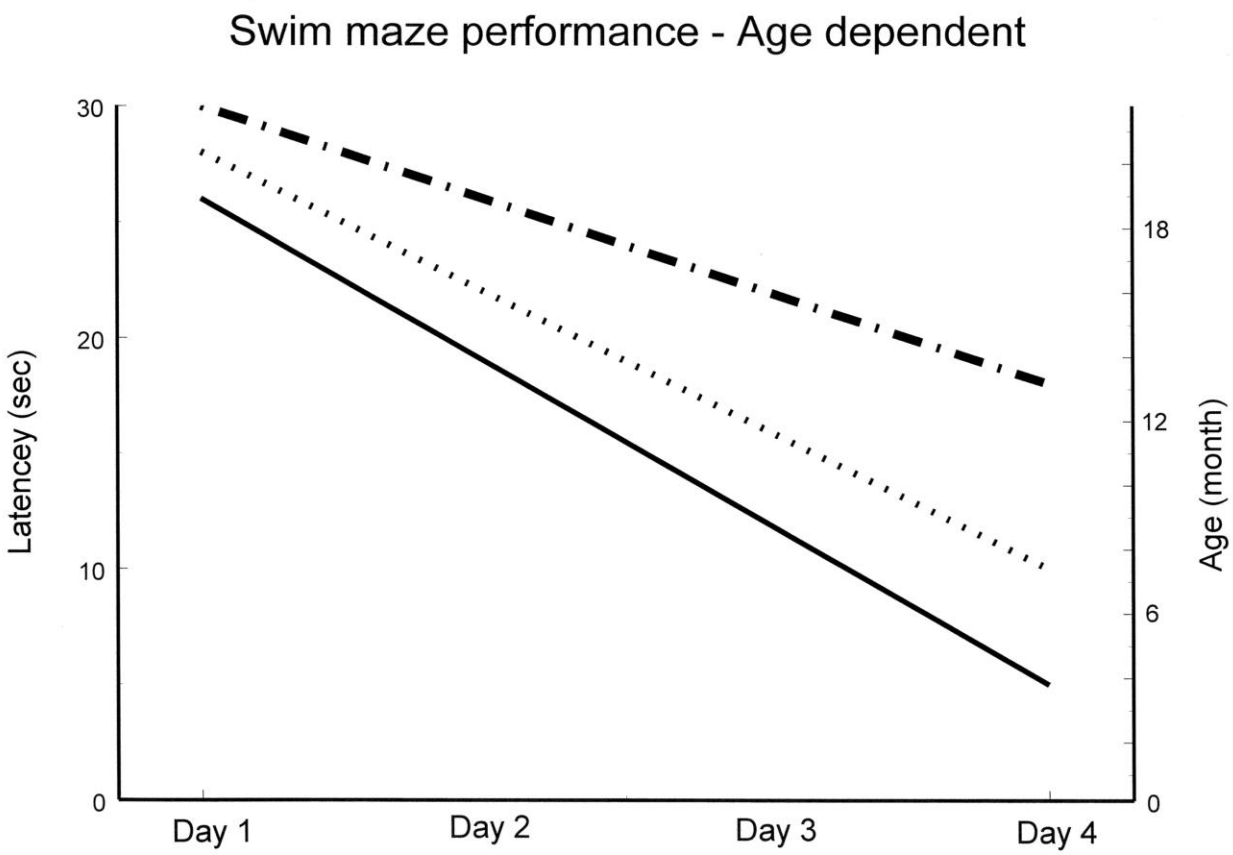
Interaction between PBDE and MeHg

Neonatal exposure – Adult spontaneous behaviour



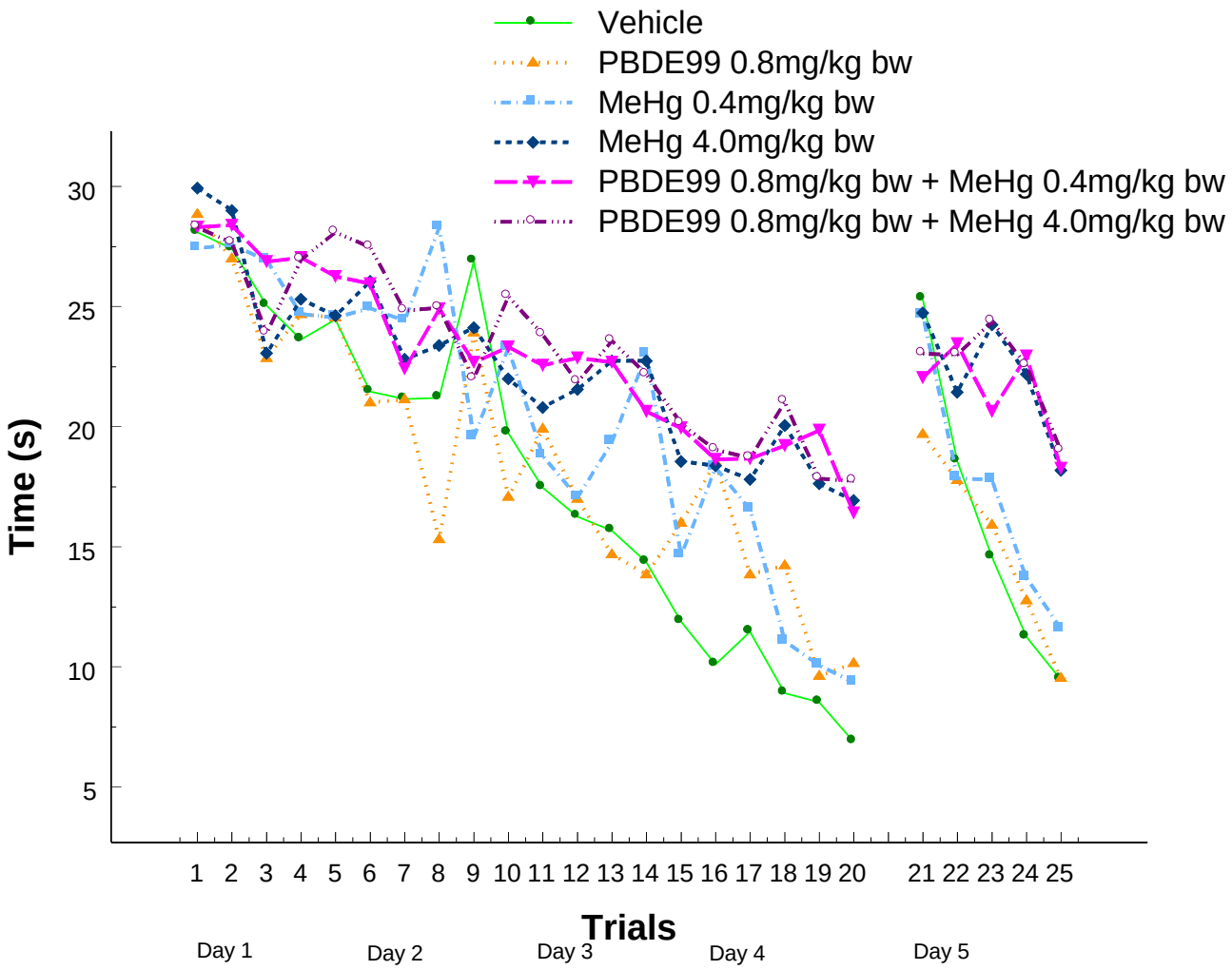
Learning and memory test





Interaction between PBDE and MeHg

Neonatal exposure – Adult performance in swim maze



Effects on nicotinic receptors [α-BTX binding (pmol/g prot.)] in 6 months old mice after neonatal exposure to PBDE 99 and MeHg

Treatment (mg/kg bw)	Hippocampus	Cerebral cortex
Vehicle	106 ± 27	66 ± 10
PBDE 99 0.8	92 ± 24	51 ± 16 *
MeHg 0.4	87 ± 21	48 ± 16 *
MeHg 4.0	81 ± 32 *	46 ± 12 *
PBDE 99 0.8 + MeHg 0.4	74 ± 22 *	47 ± 18 *
PBDE 99 0.8 + MeHg 4.0	80 ± 15 *	50 ± 9 *

Neonatal exposure to both PCB 52 and PBDE 99

- NMRI male mice

  Neonatal exposure on postnatal day 10,

  one single oral dose

  Vehicle (20% fat emulsion)

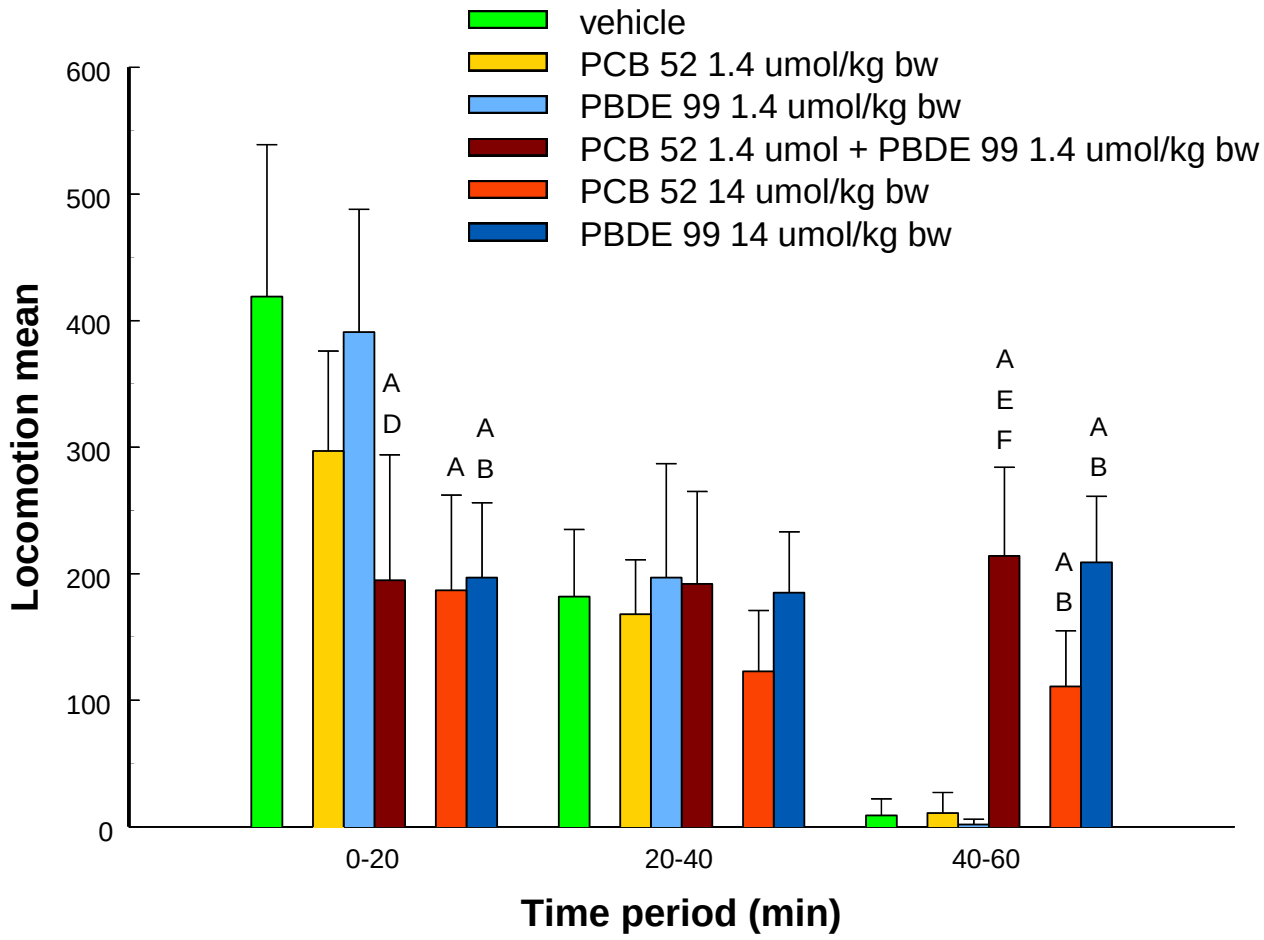
  PCB 52: 1.4 µmol/kg bw, or 14 µmol/kg bw

  PBDE 99: 1.4 µmol/kg bw, or 14 µmol/kg bw

  PCB 52 1.4 µmol/kg bw + PBDE 99 1.4 µmol/kg bw
- Spontaneous behaviour: 4-month-old

Interaction between PCB and PBDE

Neonatal exposure – Adult spontaneous behaviour



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Developmental neurotoxicity of ionizing radiation

- Ionizing radiation during gestation causes developmental neurotoxic effects (human and animal studies)
- Epidemiological studies; mental retardation from *in utero* exposure
- Epidemiological study indicate low doses of ionizing radiation (0.1 Gy) to human brain during infancy influences cognitive ability in adulthood (Hall et al., 2004)
- Animal studies, 0.4-2 Gy, during embryonic and early fetal period, affects nerve growth factors, neuronal migration, apoptosis, pruning
- ***Late fetal period and early postnatal exposure – Interaction with environmental toxicants?***

Experimental design co-exposure gamma radiation and MeHg

NMRI male mice

Neonatal exposure on postnatal day 10,

one single oral dose

Vehicle: 20% fat emulsion

MeHg: 0.40 mg/kg bw, and 4.0 mg/kg bw

Gamma radiation: 0.2 Gy, and 0.5 Gy

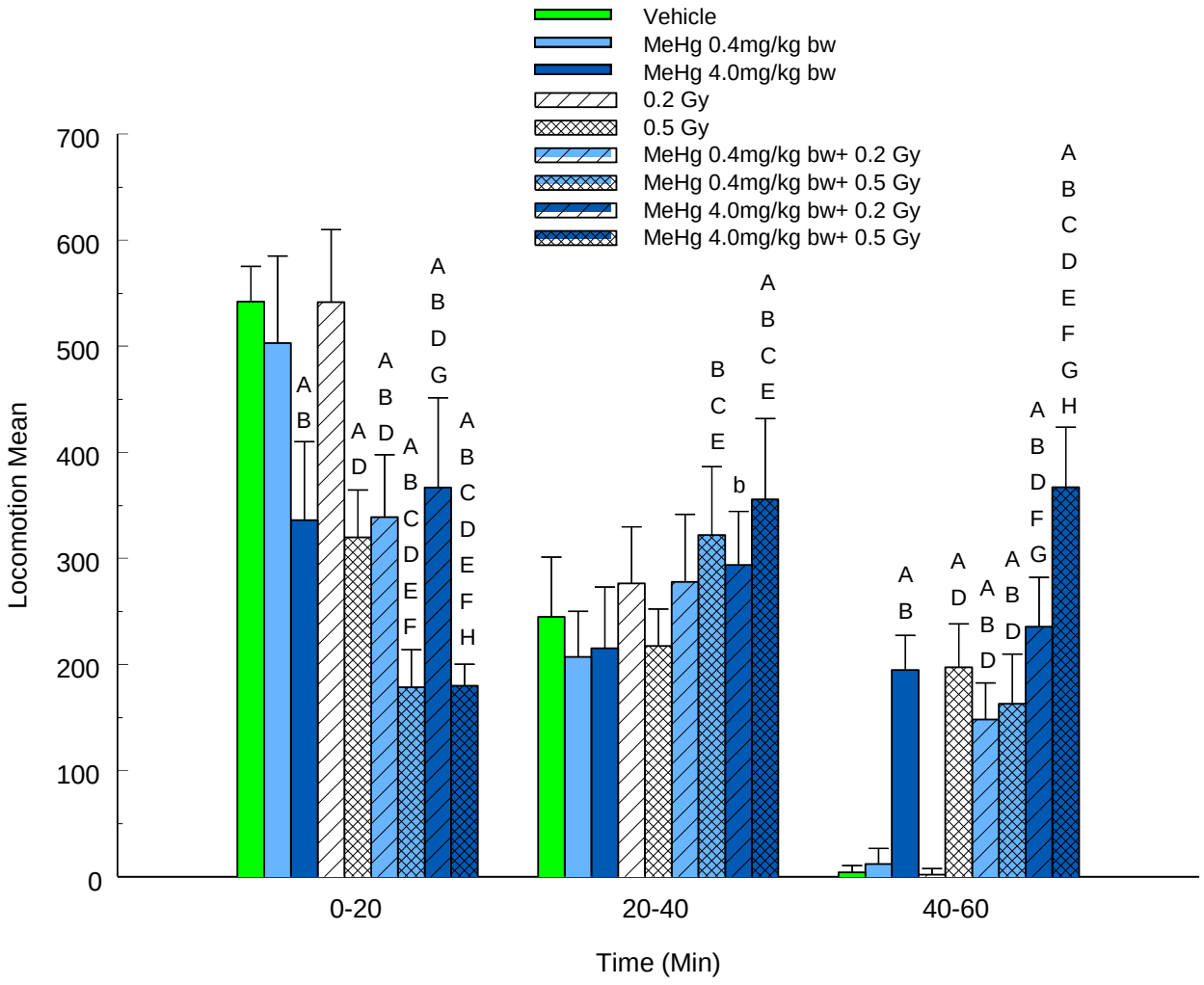
MeHg 0.4 mg/kg bw + 0.2 Gy, and MeHg 0.4 mg/kg bw + 0.5 Gy MeHg 4.0 mg/kg bw + 0.2 Gy, and MeHg 4.0 mg/kg bw + 0.5 Gy

Spontaneous behavior: 2-month-old and 4-month-old

Swim maze: 4-month-old

DEVELOPMENTAL NEUROTOXICITY TO CO-EXPOSURE MeHg AND GAMMA-RADIATION

Spontaneous behaviour, 2-month-old



Sammanfattning

- Exponering för låga doser av kemikalier och joniserande strålning kan leda till bestående beteendestörningar och försämrad funktion av det kolinerga transmittorsystemet
- Effekterna induceras under en begränsad fas av den neonatala (nyföddhetsperioden) hjärnutvecklingen
- Miljögifter kan samverka och förstärka utvecklingsneurologiska störningar
- Tidig exponering för miljögifter kan förändra känsligheten för olika ämnen i vuxen ålder (inte en nedärvd egenskap)
- Effekterna är dos – respons relaterade